RESPONSE

SUMMARY OF THE INVENTION

The present claims are directed to novel cell lines comprising a genetically engineered mutation in the mouse ortholog of a human gene. Like most patented cell lines, the described cells are useful as tumor models, for the expression of genetically engineered products, and for the identification and characterization of biochemical pathways. *Unlike* most patented cell lines, the described genetically engineered cells are totipotent embryonic stem cells. As totipotent cells, embryonic stem cells have a normal compliment of chromosomes (unlike most patented aneuploid cell lines) and can thus be introduced into an embryo (by microinjection, morula aggregation, etc.) and used to give rise to animals that are essentially wholly genetically derived from the ES cell line. When, as in the present case, the ES cell clone has been manipulated *in vitro* to contain a genetically engineered allele, the ES cell clone can be used to generate live animals capable of germline transmission of the genetically engineered allele. These animals can then be used to determine the physiological function of the mutated gene through standard genetic analysis (which discerns the normal function of a gene via which physiological systems are perturbed by the engineered alteration of gene function). In the present instance, when a certain embodiment of the claimed mutated mammalian cells (*i.e.*, an ES line embodiment) was used to produce animals homozygous for the mutation in the mouse gene that naturally encodes the exon sequence described in SEQ ID NO:294, the animals produced as taught in the specification developed cataracts at an early age. In brief, the specifically described ES cell line was used to determine that the gene mutated in the described ES cell line may present a novel means of therapeutic intervention for the treatment or prevention of, *inter alia*, cataracts (if the removal of the protein causes cataracts, logic dictates that the addition of the protein can prevent cataracts). Given the clear medical importance of vision disorders such as cataracts in western medicine (cataract surgeries generate over 4 billion dollars of revenue per year), it is clear that the above discovery clearly defines a patentable and useful invention.

In summary, a review of United States patents issued over the last several decades indicates that non-totipotent cell lines constitute patentable subject matter (5,985,290, 5,288,628, etc.), ES cell lines constitute patentable subject matter (U.S. Patent No. 6,200,806), vectors and methods of genetically manipulating ES cell lines constitute patentable subject matter (U.S. Patents Nos. 6,207,371, 6,204,061, 5,789,215, etc.), and that genetically engineered mice constitute patentable subject matter (5,948,952, 4,736,866, etc.)– and especially, as in the present case, genetically

engineered mice that define a novel modes of medical intervention. Thus, the only remaining question for the present inquiry is where and how in the above continuum of patentable scientific utility, the utility of the described ES cell line has somehow vanished?

RESPONSE

I. Status of the Claims

Claims 1, 2, and 4-7 are presently pending and presently stand as rejected under 35 USC §§101/112. No prior art rejections are presently of record. Applicants have cancelled Claim 3 and amended Claim 7. The amendment is not deemed to constitute new matter.

II. The Present Claims Are Patentable And The Rejections of Record Should Be Withdrawn.

a) Rejections Under 35 U.S.C. § 101 and §112, First Paragraph

The Examiner's rejections of Claims 1-7 under 35 U.S.C. section 101 and the intertwined rejections under section 112, first paragraph are respectfully traversed. The Examiner has apparently adopted the position that the claimed invention lacks patentable utility due to its not being supported by either a specific and/or substantial utility or a well established utility. The position articulated in The Action seems to be predicated on the flawed assumption that the specification allegedly fails to provide "...a correlation between the nucleotide sequence set forth in SEQ ID NO:294 and any gene which comprises the nucleotide sequence set forth in SEQ ID NO:294 or the protein product that it encodes."

In fact, Figure 2 (which is essentially an accession no. annotated "Index" of the Sequence Listing), at page "6 of 7", line 23 clearly discloses the database annotation corresponding to SEQ ID NO:294 (GSP W27087). The human cDNA sequence described in the above accession number had been cloned and sequenced (see, for example, published U.S. Application nos. 20020187523A1 filed by Incyte Genomics, note the effective priority date, and 2003104559 filed by Genentech), and has also been subsequently identified and annotated as derived from the gene encoding apoptosis related protein 3 ("ARP-3"). Those skilled in the art could have clearly taken the human sequences described above, and homology searched them against SEQ ID NO:294 to identify the corresponding mutated ES cell line to define the physiological role of the encoded protein. In fact, during the time spanning the filing date of the present application and the present, Applicants' employer entered into and conducted collaborative research with both of the above-named companies (among others). These leading

companies have both recognized that the physiological discoveries enabled by the broader technology embodied by the presently elected mutated cell line provides a direct path to defining the medical relevance of a given human cDNA sequence.

In this case, the described technology has shown that the encoded protein plays a role in the prevention of cataract formation in the mammalian eye. To Applicants' knowledge, no bioinformatics structure or function prediction program could have specifically enabled this discovery (yet such programs are patentable, see U.S. Patent No. 6,466,874), no "chip" based expression data could have specifically enabled this discovery (yet gene chips have a patentable utility), and no cell based assay (the topic of many patents) could have specifically enabled this discovery. It is thus puzzling why the Patent Office has apparently singled-out the one technology that *specifically* provides medically relevant *in vivo* data, as somehow not having a credible, substantial, and specific utility? Simply put, there is no credible scientific rationale for concluding that the exemplified mutated cells, employed as taught in the specification using well-established methods that are widely known in the art, (see, for example, U.S. Patent No. 6,207,371 at columns 15-16 which issued from Applic. Ser. No. 08/942,806 which was incorporated by reference into the present specification), would not produce an invention with a clear medical utility. In this case, ES cells having a mutation in the *specific* murine gene corresponding to SEQ ID NO:294 (which is merely a fragment of exon sequence that is used to identify the gene that has been functionally disrupted) have a *specific* utility in the production of mice that prematurely form cataracts. Given that here can be no question that the described genetically engineered animals define a patentable utility, how not the engineered ES cells used to generate the animals? From a practical stand point, the present quandary presents a mammalian version of the age-old chicken-or-the-egg paradox. In this case, it should be fairly clear that a patentable genetically engineered chicken would produce patentable eggs which would then produce patentable chickens.... The described cell line can be likened to such patentable eggs.

From a purely practical perspective, Applicants respectfully request that the Examiner also consider a commercial "nuts-and-bolts practical/industrial" utility for the described ES cell clones. In addition to their generation and study, the storage, handling, and transfer of genetically engineered mice is a rather expensive commercial endeavor. Unlike most academic facilities, industrial vivariums are typically run under pathogen-free "barrier" conditions and extensive efforts are undertaken to protect the pathogen free status of the various animal colonies. Consequently, new colonies being brought into the barrier are often "rederived" (often using ES cells) into the barrier via birth from "clean" surrogate

mothers animals. That's one practical use of the described ES cell clones.

Additionally, space in such facilities is often at a substantial premium. Unlike live animals, mutated ES cell clones can be stored in liquid nitrogen. Tens of thousands of mutated ES cell clones can be stored in a couple of liquid nitrogen freezers whereas many hundreds of thousands of square feet of "barrier" vivarium space would be necessary to store corresponding numbers of live mutant animal colonies. From a practical storage perspective, a couple of microtiter plates can roughly correspond to an entire room of vivarium space (the absence of such practical efficiencies largely contributed to the broader failure of the NIH's efforts to approach attack gene function through ENU mutagenesis in live mouse colonies). In brief, although the biotech utility analysis has typically focused on scientific nuances bordering on the metaphysical, the practical savings and efficiencies of working with ES cell clones provide an industrial utility that is not dissimilar from the efficiencies obtained between storing paper files as compared to digital data storage– an industrial utility clearly recognized by the U.S. Patent Office as evidenced by its recent adoption of electronic document storage. Accordingly, there can be no question of the industrial utility of the more broadly described invention as well as the specific utility of the described mutated cell line.

In view of the overwhelming evidence of the substantial, credible, specific, and well-established utility of the presently claimed invention, and in view of the absence of any evidence of record specifically refuting the utility of the described ES cell clones, the Applicants' respectfully request that the Examiner withdraw the pending rejection of Claims 1-7 under 35 U.S.C. section 101 as well as the related rejections under 35 U.S.C. section 112, first paragraph.

b) Additional Rejections under 35 U.S.C. Section 112, First Paragraph

The Examiner has also rejected Claims 1-7 under 35 U.S.C. section 112, first paragraph for allegedly failing to comply with the written description requirement. As discussed in the specification and supporting specifications incorporated by reference, those skilled in the art would understand that ***in order to generate the sequence tags described in the specification and Sequence Listing, the Applicants must necessarily be in possession of the described ES cell clones.*** Thus, there can be no scientifically credible assertion that the Applicants were not **IN ACTUAL POSSESSION** of the claimed invention. To the extent that the Examiner adamantly refuses to accept this scientific and technical fact, Applicants can deposit the ES cell line at issue with the ATCC to dispositively deal with the written description issue when and if all other remaining issues of patentability have been resolved.

As discussed above, the database accession no. clearly referenced in Figure 2 of the present specification corresponds to sequence from the human homolog of the mutated allele present within the ES cell line as identified by SEQ ID NO:294. In view of the fact that those skilled in the art had identified the human ARP-3 sequence, and could have thus determined that the described ES cell line contained a mutation in a murine homolog of the ARP-3 locus by virtue of its structural similarity to the sequence presented in SEQ ID NO:294 (which is how the exemplified ES cell line at issue was identified, catalogued, and queued for the production of the corresponding line of hyperactive mutant mice), there can be no *bona fide* question that the described ES cells were in Applicants actual possession (thus meeting the written description requirement) and enabled (since, given the rich history in the field, there can be little question that those skilled in the art could use the provided ES cells to produce corresponding mutant animals without undue experimentation).

Again, there seems to be some limited confusion over this point so it bears reiterating that the present claims are not directed to a cDNA sequences *per se*. Consequently, Applicants need not be in possession of the genus comprising SEQ ID NO:294. Conversely, as discussed above Applicants were indeed in possession of novel mammalian cell lines that encompass a mutation that disrupts the functional expression of the murine homolog of the human ARP-3 sequence (as identified using, for example, the database accession no. provided in Figure 2) which also encodes the exon sequence presented in SEQ ID NO:294. In view of the above remarks and considerations, the Examiner is respectfully requested to withdraw the pending rejection of Claims 1-7 under 35 U.S.C. §112, first paragraph for alleged want of adequate written description.

b) Rejections under 35 U.S.C. Section 112, Second Paragraph

Applicants have cancelled Claim 3 and amended Claim 7 to specifically read on mouse ES cells. Consequently, Applicants have avoided by amendment the Examiner's concerns over the scope of the word murine. The Examiner's further rejection of Claims 1-7 as indefinite are respectfully traversed. The Examiner has alleged that Claim 1 is indefinite because it is not clear how a gene corresponds to the nucleotide sequence set forth in SEQ ID NO:294. Those skilled in the relevant art would have understood that most mammalian genes contain interspersed exons and introns. Those skilled in the art also understand that mutations that disrupt the functional continuity of normal transcription, splicing, or translation of protein will typically disrupt gene function. Such disruptions can be introduced in any of a wide variety of methods, and one of the many possible methods that was specifically exemplified in

the present application integrated a retroviral-based vector that integrated within the coding region of the ARP-3 gene. This integration event functionally disrupted normal gene expression by intercepting normal ARP-3 mRNA splicing and processing (resulting in a "null" allele). In addition, the mutagenic vector employed was engineered to mediate the production of a chimeric transcript that splices to ARP-3 exon sequence located downstream from the integration site. When this downstream chimeric transcript was reverse transcribed and sequenced using 3'RACE, SEQ ID NO:294 was produced which provided a "tag" of exon ("coding") sequence data that allowed for the rapid identification of mutated genetic locus (in this case, as discussed at length above, the ARP-3 locus-- noting that the Incyte and Genentech applications had earlier provided different proprietary annotations). In view of the above explanation, Applicants respectfully submit that those skilled in the art would clearly understand that the ARP-3 (for want of a better term) genetic locus was indeed mutated in the specifically described ES cell line and that this locus indeed "encodes" (using the term in a manner similar to how ribosomal RNA or tRNA sequences are "encoded" by their corresponding genetic loci) the exon sequence presented in SEQ ID NO:294. Accordingly, the Examiner is respectfully requested to withdraw the rejections of Claims 1,2, and 4-7 under 35 U.S.C. §112, second paragraph.

To the extent that the Examiner might suggest alternative claims language that would avoid any of the above rejections, the Examiner is invited to suggest such language if it will put the claim or claims in condition for allowance.

III. CONCLUSION

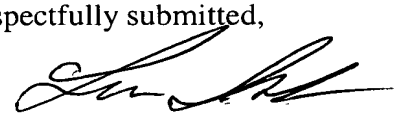
In view of the foregoing amendments and remarks, the Applicants believe that the application is in good and proper condition for allowance. Early notification to that effect is earnestly solicited.

If the Examiner feels that a telephone call would expedite the consideration of the application, the Examiner is invited to call the undersigned attorney at (281) 863-3333. The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 50-0892 for any matter in connection with this response, including fees for any extension of time, which may be required.

VII. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Paras have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,



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Date

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